REMARKS

Claims 1-5 and 8-34 are pending in the application. The present invention relates to methods of measuring the level of lipid peroxidation in a mammal suspected of having Alzheimer's Disease (claims 1-5 and 8-10), methods to diagnose oxidant stress syndrome (Alzheimer's Disease) in a mammal (claims 11-12), methods of measuring the level of an isoprostane marker for lipid peroxidation in a mammal (claims 13-19), methods of identifying a compound useful for treatment of Alzheimer's Disease (claims 20-23), methods of determining the optimal concentration and dosage frequency of such a compound (claims 24-28), methods of identifying a compound useful for reducing the level of an isoprostane molecular marker for lipid peroxidation (claims 29-32) and kits for diagnosing Alzheimer's Disease in a mammal or for measuring the level of an isoprostane molecular marker for lipid peroxidation in a mammal (claims 33 and 34).

Preliminarily, in the Advisory Action, the Examiner has indicated that the Information Disclosure Statement does not meet the requirements for an after final submission. Accordingly, Applicants submit herewith the identical Supplemental Information Disclosure Statement and accompanying 1449 form citing all of the art Applicants believe is relevant, including Applicants' own work.

Rejection of claims 1-5 and 8-34 pursuant to 35 U.S.C. § 112, first paragraph

Claims 1-5 and 8-34 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. In the Examiner's opinion, the specification does not provide a written description of any compounds found for effectively treating Alzheimer's Disease, and no other treatments for isoprostane elevating disorders are shown. Further, the Examiner states that no kits are seen. The Examiner also contends that the claims are not taught by the specification as originally filed and much more than routine experimentation would be required to make and use the invention. In the Examiner's view, while screening for drugs is routine, screening for drugs that are useful for treatment of Alzheimer's Disease is not routine. The Examiner also contends that the specification does not include a teaching of how to make and use the claimed processes because there is only speculation and conjecture set forth in the specification regarding the processes, and no specifics or examples of how to perform the claimed processes are provided.

Applicants respectfully traverse the rejection of claims 1-5 and 8-34, under 35 U.S.C. § 112, first paragraph, for the reasons set forth below.

Applicants' invention includes the identification of a relationship between the level of lipid peroxidation (as measured by the level of isoprostane markers) and an oxidative stress syndrome such as Alzheimer's Disease. It is Applicant's contention, fully supported by the specification, that this connection is described and enabled in the specification, and therefore the specification and claims meet all of the requirements of 35 U.S.C. § 112, first paragraph.

In addition, Applicants further submit herewith the post-filing reference of Pratico et al. (2000, Ann. Neurol. 48:809-812) which demonstrates that the invention has been further reduced to practice by Applicants whereby the same methods as those included in the application were utilized to arrive at the results predicted in the as-filed application. This reference provides evidence that the disclosure of the as-filed specification enables the claimed invention, and argues against the Examiner's assertion that the specification contains "only speculation and conjecture" regarding the present invention. This reference is not prior art to the present application, but rather represents post-filing reduction to practice of the present invention. The contents of this reference are more fully discussed below.

As an initial matter, it is well-settled that an applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 882 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such a manner that one of skill in the art will be able to practice it without undue experimentation (*In re Borkowski*, 422 F.2d at 908), and "representative samples are not required be the statute and are not an end in themselves" (*In re Robbins*, 429 F.2d 452, 456-457, 166 USPQ 522, 555 (CCPA 1970)). Thus, 35 U.S.C § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferable omits that which is well-known to those skilled in the art and is already available to the public. MPEP

§2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed, as long as it is not undue.

Thus, in view of the recited legal standard, under the present patent law, claims 1-5 and 8-34 are amply enabled by the specification as filed under 35 U.S.C. §112, first paragraph. The specification amply supports these claims because the skilled artisan, armed with the methods and the markers disclosed in the specification, would have been able to measure lipid peroxidation in a mammal, diagnose Alzheimer's disease in a mammal, measure the level of an isoprostane molecular marker in a mammal, identify a compound useful for reducing the level of an isoprostane marker for lipid peroxidation molecular marker for lipid peroxidation in the tissue of a mammal, identify an effective amount, optimal concentration, or optimal dosage frequency of a compound useful for the treatment of Alzheimer's disease in a mammal, and make kits for measuring isoprostane markers in tissue and bodily fluids and for diagnosing Alzheimer's disease as recited in the claims, and to practice the invention commensurate with the scope of the claims without undue experimentation. In addition, the post-filing reference of Pratico et al. in fact further demonstrates reduction to practice of the claimed invention, and that the as-filed specification is enabled for the claimed invention.

The specification fully supports the invention of claims 1-5 and 8-10, which pertains to a method for measuring the level of lipid peroxidation in a mammal suspected of having Alzheimer's disease (AD). It is well-known in the art that isoprostanes are molecular makers of lipid peroxidation both *in vitro* and *in vivo* (see, for example, Patona and Fitzgerald, 1997, Arterioscl. Thromb. Biol. 17:2309-2315). Applicants submit, without limiting the invention in any way, that Example 2 in the specification as filed demonstrates the use of Gas Chromatography / Mass Spectrometry as a method of measuring the levels of a isoprostane isomer. Further, Figures 5 and 6 demonstrate that levels of 8,12-*iso*-iP$F_{2\alpha}$-VI were greater in patients with a clinical diagnosis of probable and possible AD compared to control groups. For example, beginning in line 20 of page 34, the specification discloses that patients with a clinical diagnosis of AD exhibit increased lipid peroxidation levels in cerebrospinal fluid (CSF), plasma and urine samples. Thus the specification as filed teaches a correlation between increased lipid peroxidation levels with risk factors known in the art for AD.

Applicants also submit that Pratico et al. (2000, Ann. Neurol. 48:809-812) demonstrates post-filing reduction to practice of the present invention. Pratico et al. demonstrates that patients having clinical diagnosis of AD have increased CSF, plasma, and urinary levels of 8,12-*iso*-iPF$_{2\alpha}$-VI, which is a reliable marker of *in vivo* lipid peroxidation, and there is a correlation between the levels of 8,12-*iso*-iPF$_{2\alpha}$-VI and the severity of the dementia in AD patients. In addition, Pratico et al. demonstrates that CSF tau increases and Aβ_{1-42} decreases with progression of the disease in AD patients. Therefore, the results of Pratico et al. demonstrate that the specification as-filed is in fact enabled for the claimed invention because Pratico et al. provides a direct correlation of CSF 8,12-*iso*-iPF$_{2\alpha}$-VI levels and CSF tau, and an inverse correlation of these levels with CSF Aβ_{1-42} in AD patients. Thus, elevations in the level of 8,12-*iso*-iPF$_{2\alpha}$-VI not only reflect an increase in central nervous system oxidative stress, but also correlate with the progression of Alzheimer's disease. The results described in the post-filing reference of Pratico et al. are predicted in the specification as filed. For example, beginning on line 15 of page 24 in the specification, "CSF isoprostane levels correlate directly with CSF-tau protein and the Dementia Severity Rating Scale (DSRS) and inversely with the percentage of CSF Aβ_{1-42} and the Mini Mental State Examination (MMSE)" is recited.

Accordingly, Applicants respectfully submit that claims 1-5 and 8-10 as they pertain to a method of measuring the level of lipid peroxidation in a mammal suspected of having Alzheimer's Disease are enabled by the specification as filed, in view of the data contained in the post-filing reference of Pratico et al. Applicants contend that Pratico demonstrates reduction to practice of the instant invention by arriving at the results disclosed in the as-filed specification by following the same methods as those disclosed said specification. Therefore, Applicants request that the rejection of claims 1-5 and 8-10 pursuant to 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Applicants respectfully submit that the specification as filed also fully supports the invention of clams 11-12, which pertains to a method of diagnosing Alzheimer's disease in a mammal. The alleged absence of disclosure of specific compounds and methods useful for treating Alzheimer's diseases has no bearing on the enablement of these claims because the invention pertains to diagnosing Alzheimer's disease, not treating Alzheimer's disease. As described elsewhere herein, Applicants assert that Example 2 is a working example wherein the method of the invention was used to measure the levels of isoprostane markers in the

cerebrospinal fluid, urine and plasma of patients suspected of having Alzheimer's disease. Further, as discussed elsewhere herein, the post-filing reference of Pratico et al. discloses the same methods as those included in the specification as filed, and arrives at the same results as disclosed in the specification. Therefore, this reference provides evidence that the as-filed specification is in fact enabled for claims 11-12 relating to a method of diagnosing a disease in a mammal. Accordingly, Applicants respectfully request that the rejection of claims 11-12 pursuant to 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Applicants respectfully submit that the specification fully supports the invention of claims 13-19, which pertains to a method for measuring the level of an isoprostane marker in a mammal using a step utilizing a total lipids extraction method. The alleged absence of disclosure of specific compounds and methods useful for treating Alzheimer's diseases has no bearing on the enablement of the invention of these claims because the invention pertains to measuring an isoprostane marker, not treating Alzheimer's disease. The specification fully supports the enablement of these claims. Example 1 is a working example wherein total lipids were extracted from tissue to isolate and effectively measure isoprostane molecular markers in brain tissue (specification, page 29, lines 5-12). The specification further discloses how the total lipid extraction method can be adapted to measure isoprostane molecular markers in bodily fluids (specification, page 18, line 31 through page 19, line 5). Therefore, the specification fully supports the use of a method for measuring the level of an isoprostane marker in a mammal using a step utilizing a total lipids extraction method without undue experimentation. Accordingly, Applicants respectfully request that the rejection of claims 13-19 pursuant to 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Applicants respectfully submit that the specification fully supports the invention of claims 29-32, which pertains to a method for identifying a compound useful for reducing the level of an isoprostane molecular marker for lipid peroxidation in the tissue of a mammal, and the invention of claims 20-23, which pertains to a method for identifying a compound useful for the treatment of Alzheimer's disease in a mammal. The "treatment of Alzheimer's disease" is defined in the specification to include "alleviating one or more of its symptoms" (specification, page 12, line 24). The specification discloses that one of the symptoms of Alzheimer's disease is an increase in isoprostane molecular markers in the tissues and body fluids of Alzheimer's patients (specification, page 30, paragraph 1, and page 36, line 30 to page 37, line 1). Further,

Pratico et al. demonstrates the post-filing reduction to practice of measuring isoprostane as a clinical diagnosis of AD. Pratico et al. discloses that patients with a clinical diagnosis of AD have increased CSF, plasma, and urinary levels of 8,12-*iso*-iPF$_{2\alpha}$-VI. Therefore, a compound useful for treating Alzheimer's disease is one that reduces the level of an isoprostane molecular marker in the tissues and body fluids of a patient. The specification fully supports the enablement of these claims in view of the post-filing reference of Pratico et al. The specification further discloses specific compounds that inhibit lipid peroxidation *in vivo*, i.e. vitamin E, vitamin C, ibuprofen and aspirin, and suggested dosage levels (see specification, page 19, line 20 to page 20, line 8) that one of skill in the art could use as guidance of specific compounds and treatment methods to use with the screening method of claims 29-32. Further, compounds similar in structure and/or biological effect and their methods of their use are well known in the art. One of skill in the art would therefore be able to determine the dosages and treatment methods for similar compounds without undue experimentation (see, MPEP § 2164.01(c)). One of skill in the art could also easily combine the methods to measure the levels of isoprostane molecular markers in tissues and body fluids of a mammal with what is well-known in the art and disclosed in the specification regarding specific compounds and treatment methods to successfully practice without undue experimentation the method of claims 29-32 for identifying a compound useful for reducing the level of an isoprostane molecular marker for lipid peroxidation in the tissue of a mammal. Accordingly, Applicants respectfully request that the rejection of claims 29-32 pursuant to 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

The specification fully supports the invention of claims 24-28, which pertains to a method for identifying an effective amount, optimal concentration, or optimal dosage frequency of a compound useful for a treatment of Alzheimer's disease in a mammal. As discussed elsewhere herein, Example 2 is a working example wherein the levels of isoprostane markers were measured in the cerebrospinal fluid, urine and plasma of patients suspected of having Alzheimer's disease, and the level of an isoprostane marker is shown to be significantly higher in a patient suspected of having Alzheimer's disease than in a patient not suspected of having Alzheimer's disease. Further, Pratico et al. demonstrates post-filing reduction to practice of the claimed invention. Pratico et al. establishes the connection between Alzheimer's disease and elevated levels of isoprostane molecular markers in the body fluids and tissues. Therefore,

the specification in view of Pratico et al. fully supports the use of the methods for identifying the effective amount, optimal concentration, or optimal dosage frequency of a compound useful for the treatment of Alzheimer's disease in a mammal without undue experimentation. Accordingly, Applicants respectfully request that the rejection of claims 24-28 pursuant to 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

The specification fully supports the invention of claims 33 and 34, which pertain to kits for measuring isoprostane molecular markers in tissue and body fluids, and for diagnosing Alzheimer's disease. As discussed elsewhere herein, the specification in view of Pratico et al. fully supports the connection between Alzheimer's disease and elevated levels of isoprostane molecular markers in the body fluids and tissues. The alleged absence of disclosure of specific compounds and methods useful for treating Alzheimer's disease has no bearing on the enablement of these claims because the invention pertains to measuring isoprostane molecular markers and diagnosing Alzheimer's disease, not treating Alzheimer's disease. The Examiner alleges that no kits are seen in the specification; however this is not the case. The components of and kits are disclosed in the specification (pages 25-27), and are recited in claims 33 and 34 as filed. Further, Examples 1 and 2 provide the disclosure of how to use the kits to measure isoprostane markers or diagnose Alzheimer's disease. Therefore, the specification fully supports making and using the kits for measuring isoprostane molecular markers in tissue and body fluids, and for diagnosing Alzheimer's disease without undue experimentation. Accordingly, Applicants respectfully request that the rejection of claims 33-34 pursuant to 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Applicants respectfully submit that claims 1-5 and 8-34 are amply supported by the numerous working examples provided in the specification as filed, as demonstrated by the post-filing reference of Pratico et al., wherein the results are arrived using the same methods as disclosed in the specification as filed. Thus, Applicants respectfully request that the rejection of claims 1-5 and 8-34 be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that each of currently pending claims 1-5 and 8-34 is in condition for allowance. Reconsideration and allowance of claims 1-5 and 8-34 are respectfully requested at the earliest possible date.

Respectfully submitted,

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August 27, 2007
(Date)

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Supplemental IDS and Form 1449.
Copy of Pratico et al., 2000, Ann. Neurol. 48:809-812.